Drug Discovery Strategies to Reduce the Selection of Resistance

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Effective drug discovery strategies to reduce the probability of bacterial drug resistance are available today. Bacterial drug resistance has different definitions, including genetic mutations and molecular changes, MIC increases, and impact on clinical outcome. These criteria vary, but resistance is most often correlated to a significant increase in MIC value. Resistance has developed to every class of effective antibacterial therapeutic. Effective strategies practiced in drug discovery can reduce the probability of resistance. Antibacterial drugs that target that the products of multiple genes, or drugs that attack different targets appear to be key in controlling resistance. All of the successful monotherapy targets – penicillin binding proteins, ribosomal RNA, topoisomerases, peptidoglycan cell wall, and bacterial membrane - appear to be the product of multiple genes, or have multiple targets that are inhibited by the therapeutic. The next generations of bacterial drugs are all improvements on existing molecules, with either added functionality within the pharmacophore class, dual target molecules, or hybrid molecules consisting of two different linked classes. Combination therapy in which two or more antibacterial drugs with different targets are combined is also a proven method to reduce the generation of resistance. Novel targets, with new functionality not utilize before, are unlikely to have a dramatic impact on the near future. Caution should be used with novel targets for which there exists no natural inhibitor, since this may signal frequent resistance mechanisms. Successful drug discovery groups are based around vetted targets or pharmacophore-classes of antibacterials, with an emphasis on medicinal chemistry and integrated biological investigations to determine the potential of the next generation of antibacterial compounds.